**INFORMATION DISCLOSURE STATEMENT**

In accordance with their duty of disclosure under 37 C.F.R. §1.56 and §1.97 (a)-(b), applicants would like to direct the Examiner's attention to the following documents:

1. U.S. Patent No. 5,688,653, November 18, 1997 (Ulrich, et al.) **(Exhibit 1)**;

2. Baynes, J. W. (1991). Role of oxidative stress in development of complications in diabetes. Diabetes 40:405-412 **(Exhibit 2)**;

3. Borchelt, D. R., et al. (1996). Familial Alzheimer's Disease-linked presenilin 1 variants elevate Aβ1-42/1-40 ratio *in vitro* and *in vivo*. Neuron 17: 1005-1013 **(Exhibit 3)**;

4. Brett, J., et al. (1993). Survey of the distribution of a newly characterized receptor for advanced glycation end products in tissues. Am. J. Pathol. 143(6):1699-1712 **(Exhibit 4)**;

5. Brownlee, M. (1992). Glycation products and the pathogenesis of diabetic complications. Diabetes Care 15(12):1835-1842 **(Exhibit 5)**;

6. Cai, X-D., et al. (1993). Release of excess amyloid β protein from a mutant amyloid β protein precursor. Science 259: 514-516 **(Exhibit 6)**;

7. Citron, M., et al. (1997). Mutant presenilins of Alzheimer's Disease increase production of 42-residue amyloid β-protein in both transfected cells and transgenic mice. Nature Medicine 3(1): 67-72 **(Exhibit 7)**;

8. Dell'Angelica, E.C., et al. (1994). Primary structure and binding properties of calgranulin C, a novel S100-like calcium-binding protein from pig granulocytes. J. Biol. Chem. 269: 28929-28936 **(Exhibit 8)**;

9. Fahey, T., et al. (1991). Diabetes impairs the late inflammatory response to wound healing. J. Surg. Res. 50: 308-313 **(Exhibit 9)**;

10. Fu, M-X., et al. (1996). The advanced glycation end product, $N^{\varepsilon}$-(carboxymethyl)lysine, is a product of both lipid peroxidation and glycoxidation reactions. J. Biol. Chem. 271: 9982-9986 **(Exhibit 10)**;

11. Giardino, I., et al. (1994). Nonenzymatic glycosylation *in vitro* and in bovine endothelial cells alters basic fibroblast growth factor activity. J. Clin. Invest. 94: 110-117 **(Exhibit 11)**;

12. Gibbons, G. H. and V. J. Dzau. (1996). Molecular therapies for vascular diseases. Science 272: 689-693. **(Exhibit 12)**;

13. Khoury, J. E., et al., (1994). Macrophages adhere to glucose-modified basement membrane collagen IV via their scavenger receptors. J. Biol. Chem. 269: 10197-10200 **(Exhibit 13)**;

14. Kuo, Y-M., et al. (1996). Water-soluble Aβ (N-40, N-42) oligomers in normal and Alzheimer Disease brains. J. Biol. Chem. 271(8): 4077-4081 **(Exhibit 14)**;

15. Lander, H. M., et al. (1997). Activation of the receptor for advanced glycation end products triggers a $p21^{ras}$ dependent mitogen-activated protein kinase pathway regulated by oxidant stress. J. Biol. Chem. 272: 17810-17814 **(Exhibit 15)**;

16. Ledesma, M. D., et al. (1994). Analysis of microtubule-associated protein tau glycation in paired helical filaments. J. Biol. Chem. 269(34):21614-21619 **(Exhibit 16)**;

17. Li, J. and A.M. Schmidt (1997). Characterization and functional analysis of the promoter of RAGE, the receptor for advanced glycation end products. J. Biol. Chem. 272: 16498-16506 **(Exhibit 17)**;

18. Lorenzo, A. and B.A. Yanker (1994). β-amyloid neurotoxicity requires fibril formation and is inhibited by Congo red. Proc. Nat. Acad. Sci. USA 91: 12243-12247 **(Exhibit 18)**;

19. Mattson, M. P. and Y. Goodman (1995). Different amyloidogenic peptides share a similar mechanism of neurotoxicity involving reactive oxygen species and calcium. Brain Res. 676: 219-224 **(Exhibit 19)**;

20. Miyata, T., et al. (1996). The receptor for advanced glycation end products (RAGE) is a central mediator of the

interaction of AGE-β2 Microglobulin with human mononuclear phagocytes via an oxidant-sensitive pathway. J. Clin. Invest. 98: 1088-1094 **(Exhibit 20)**;

21. Nakamura, Y., et al. (1993). Immunohistochemical localization of advanced glycosylation endproducts in coronary atheroma and cardiac tissue in diabetes mellitus. Am. J. Pathol. 143(6): 1649-1656 **(Exhibit 21)**;

22. Neeper, M., et al. (1992). Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. J. Biol. Chem. 267: 14998-15004 **(Exhibit 22)**;

23. Palinski, W., et al. (1995). Immunological evidence for the presence of advanced glycosylation end products in atherosclerotic lesions of euglycemic rabbits. Arterioscl. Thromb. and Vasc. Biol. 15(5): 571-582 **(Exhibit 23)**;

24. Park, L., et al. (1998). Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nature Medicine 4: 1025-1031 **(Exhibit 24)**;

25. Park, L., et al. (1997). A murine model of accelerated diabetic atherosclerosis: suppression by soluble receptor for advanced glycation endproducts. Circulation Supplement. Abstract 3079 **(Exhibit 25)**;

26. Reddy, S., et al. (1995). $N^{\epsilon}$-(Carboxymethyl)lysine is a dominant advanced glycation end product (AGE) antigen in

tissue proteins. Biochemistry 34: 10872-10878 **(Exhibit 26)**;

27. Renard, C., et al. (1997). Recombinant advanced glycation end product receptor pharmacokinetics in normal and diabetic rats. Mol. Pharm. 52: 54-62 **(Exhibit 27)**;

28. Roher, A. E., et al. (1996). Morphology and toxicity of Aβ-(1-42) dimer derived from neuritic and vascular amyloid deposits of Alzheimer's Disease. J. Biol. Chem. 271(34): 20631-20635 **(Exhibit 28)**;

29. Schleicher, E. D., et al. (1997). Increased accumulation of the glycoxidation product $N^{\epsilon}$-(carboxymethyl)lysine in human tissues in diabetes and aging. J. Clin. Invest. 99: 457-468 **(Exhibit 29)**;

30. Schmidt, A. M., et al. (1995). Advanced glycation endproducts interacting with their endothelial receptor induce expression of vascular cell adhesion molecule-1 (VCAM-1) in cultured human endothelial cells and in mice. J. Clin. Invest. 96: 1395-1403 **(Exhibit 30)**;

31. Schmidt, A. M., et al. (1994). Receptor for advanced glycation endproducts (AGEs) has a central role in vessel wall interactions and gene activation in response to circulating AGE proteins. Proc. Nat'l Acad. Sci. USA 91: 8807-8811 **(Exhibit 31)**;

32. Schmidt, A. M., et al. (1992). Isolation and characterization of two binding proteins for advanced

glycosylation end products from bovine lung which are present on the endothelial cell surface. J. Biol. Chem. 267: 14987-14997 **(Exhibit 32)**;

33. Schmidt, A. M., et al. (1994). Cellular receptors for advanced glycation end products. Arterioscler. Thromb. 14:1521-1528 **(Exhibit 33)**;

34. Schmidt, A. M., et al. (1995). The dark side of glucose. (News and Views). Nature Medicine 1: 1002-1004 **(Exhibit 34)**;

35. Schmidt, A. M., et al. (1993). Regulation of human mononuclear phagocyte migration by cell surface-binding proteins for advanced glycation end products. J. Clin. Invest. 92: 2155-2168 **(Exhibit 35)**;

36. Schmidt, A. M., et al. (1997). The V-domain of receptor for advanced glycation endproducts (RAGE) mediates binding of AGEs: a novel target for therapy of diabetic complications. Circulation Supplement 96:#194, p. I-37 **(Exhibit 36)**;

37. Schmidt, A. M., et al. (1994). The endothelial cell binding site for advanced glycation end products consists of a complex: an integral membrane protein and a lactoferrin-like polypeptide. J. Biol. Chem. 269: 9882-9888 **(Exhibit 37)**;

38. Soulis, T., et al. (1997). Advanced glycation end products and their receptors co-localise in rat organs susceptible

to diabetic microvascular injury. Diabetologia 40: 619-628 **(Exhibit 38)**;

39. Turner, R.S., et al. (1997). Amyloids $\beta_{40}$ and $\beta_{42}$ are generated intracellularly in cultured human neurons and their secretion increases with maturation. J. Biol. Chem. 271(15): 8966-8970 **(Exhibit 39)**;

40. Vitek, M.P., et al. (1994). Advanced glycation end products contribute to amyloidosis in Alzheimer disease. Proc. Nat'l Acad. Sci. USA 91: 4766-4770 **(Exhibit 40)**;

41. Vlassara, H., et al. (1995). Identification of galectin-3 as a high-affinity binding protein for advanced glycation end products (AGE): a new member of the AGE-receptor complex. Molec. Med. 1: 634-646 **(Exhibit 41)**;

42. Vlassara, H., et al. (1994). Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. Lab. Invest. 70: 138-151 **(Exhibit 42)**;

43. Wautier, J.-L., et al. (1996). Receptor-mediated endothelial cell dysfunction in diabetic vasculopathy: soluble receptor for advanced glycation end products blocks hyperpermeability in diabetic rats. J. Clin. Invest. 97: 238-243 **(Exhibit 43)**;

44. Wautier, J.-L., et al. (1996). Interaction of diabetic erythrocytes bearing advanced glycation endproducts with the endothelial receptor AGE induces generation of reactive

oxygen intermediates and cellular dysfunction. Circulation Supplement 94(8): #4139 **(Exhibit 44)**;

45. Wu J., et al. (1997). The soluble receptor for advanced glycation endproducts (sRAGE) ameliorates impaired wound healing in diabetic mice. Plastic Surg. Res. Council Abstract #77, p. 43 **(Exhibit 45)**.

46. Yan, S. D., et al. (1994). Enhanced cellular oxidant stress by the interaction of advanced glycation end products with their receptors/binding proteins. J. Biol. Chem. 269: 9889-9897 **(Exhibit 46)**;

47. Yan, S. D., et al. (1996). RAGE and amyloid-β peptide neurotoxicity in Alzheimer's disease. Nature 382: 685-691 **(Exhibit 47)**;

48. Yan, S. D., et al. (1997). Amyloid-β peptide-receptor for advanced glycation endproduct interaction elicits neuronal expression of macrophage-colony stimulating factor: a proinflammatory pathway in Alzheimer disease. Proc. Nat'l Acad. Sci. 94: 5296-5301 **(Exhibit 48)**.

The above-listed documents are again listed on PTO Form 1449 attached hereto as **Exhibit A**. Above-listed references 1, 22, 24, and 27 were cited in the International Search Report in connection with PCT International Application No. PCT/US99/23303, filed October 6, 1999. A copy of the International Search Report is attached hereto as **Exhibit B.**

Copies of the above-listed documents are attached hereto as

**Exhibits 1-48**. Applicants request that the Examiner make the above-listed documents of record in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone at the number provided below.

No fee other than the enclosed SIX HUNDRED SEVENTY-FIVE DOLLAR ($675.00) fee is deemed necessary in connection with the filing of this Amendment and Information Disclosure Statement. If any other fee is required, however, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

9/25/00

John P. White
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Date